PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
23725 PC 1		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK00/00425	27/07/2000	27/07/1999
International Patent Classification (IPC) or national classification and IPC A61K38/00		
Applicant HEMEBIOTECH A/S et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 205 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27/02/2001	18.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fayos, C Telephone No. +49 89 2399 2180

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK00/00425

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

139-144	as originally filed			
1-138	as received on	02/10/2000	with letter of	19/09/2000

Claims, No.:

1-53	with telefax of	01/03/2001

Drawings, sheets:

1/49-49/49	as received on	02/10/2000	with letter of	19/09/2000

Sequence listing part of the description, pages:

1-11, filed with the letter of 19.09.2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.
   ☒ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 17 and 22 (completely); 1-16, 18-21, 23-33, 34-42 and 43-44 (partially).

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 17 and 22

(completely); 1-16, 18-21, 23-33, 34-42 and 43-44 (partially) are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16, 18-21, 23-53
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-16, 18-21, 23-53
Industrial applicability (IA)	Yes:	Claims	1-16, 18-21, 23-53
	No:	Claims	-

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item II

Priority

2- The priority date (27.07.1999) appears to be valid for the subject matter claimed. Hence, D4 is not prior art in this case. If it turns out that it is not correct, the document D4 cited in the international search report could become relevant.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

4- Claim 1 is not supported by the description as required by Article 6 PCT, as its scope is broader than justified by the description and drawings. The present application only provides technical support for the use of PBGD for the manufacture of a medicament for the treatment or prophylaxis of AIP.

Therefore, claims 1-3 have been read as if they were restricted to AIP (claim 2) and PBGD (claim 3) for the purpose of this opinion. Hence, only a partial opinion on novelty, inventive step and industrial applicability will be given for the subject matter of claims 1-3 and the corresponding dependent claims.

The same applies to claims 34-35 (and their corresponding dependent claims) and to claim 43.

5- Claims 17 and 22 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved (i. e. "so as to enhance the half-life thereof in the subject's bloodstream" and "formulated in such a manner that it exerts at least part of its enzymatic activity intracellularly upon administration to the subject", respectively) which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result are missing.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

6- Reference is made to the following documents:

D1: GROSS U ET AL: 'Haem precursors and porphobilinogen deaminase in erythrocytes and lymphocytes of patients with acute intermittent porphyria' CELLULAR AND MOLECULAR BIOLOGY,US,TARRYTOWN, NY, vol. 43, no. 1, 1 February 1997 (1997-02-01), pages 29-35, XP002082339 ISSN: 0145-5680

D2: SASSA S: 'Diagnosis and therapy of acute intermittent porphyria' BLOOD REVIEWS,GB,EDINBURGH, vol. 10, no. 1, 1 March 1996 (1996-03-01), pages 53-58, XP002082340

D3: GRANDCHAMP B: 'Acute intermittent porphyria' SEMINARS IN LIVER DISEASE,DE,STUTTGART, vol. 18, no. 1, 1 January 1998 (1998-01-01), pages 17-24, XP002082341

D4: see item VI

6.1- Additional document:

D5: MOLECULAR CELL BIOLOGY (Third edition- 1995) p 299-300

NOVELTY - Art. 33 (1) and (2) PCT

7- Claims 1-16, 18-21 and 23-53 appear to be novel in the light of the prior art cited in the search report (see restrictions item III):

7.1- The novel features are:

- the use of PBGD for the preparation of a pharmaceutical composition for the treatment or prophylaxis of AIP (claims 1-16, 18-21 and 23-42),
- PBGD for use as a medicament (claims 43-44),
- an expression plasmid as in claim 45,
- a DNA fragment as in claim 46,
- a production strain of rhPBGD as in claim 47,
- a method for the preparation of rhPBGD as in claims 48-51, and
- a rhPBGD as in claim 52 or claim 53.

INVENTIVE STEP - Art. 33 (1) and (3) PCT

8- Claims 1-16, 18-21 and 23-53 lack inventive step for the reasons stated below:

8.1- The closest prior art is represented by D2, which mentions methods of treatment of AIP (see p 58 c 1 §2) and by D3, which also discloses methods of treatment and prevention of AIP (see p 22 c 1 § 2-3).

The closest prior art differs from the present application in that it does not mention the use of PBGD as a medicament, for the treatment of AIP.

The technical effect achieved in the present application is the effective treatment / prophylaxis of AIP.

The objective problem posed in the present application is alternative (better) means for the treatment of AIP.

The solution proposed is the use PBGD.

Said solution is obvious, as shown below.

8.2- It is well known (see any of D1-D3) that AIP is an autosomal dominant disorder resulting from a patrial porphobilinogen deaminase (PBGD) deficiency. Furthermore, the gene coding for PBGD has been identified, its cDNA has been cloned and the mutations which cause AIP are also known (see D2 and D3).

It would therefore be obvious for the skilled man, to compensate the deficiency in PBGD in a subject by administrating PBGD (directly, or by means of gene therapy) and hence normalize the levels of PBGD in said subject.

The concept underlying the present application lacks therefore inventive step (deficiency of an enzyme treated by administrating said enzyme by means of e. g. gene therapy - well known, see e. g. D2 p 22 c 2 "future prospects" and additional document D5)

8.3- The features of claims 4-16, 18-21, 23-33, 37-42 and 44-53 are merely some of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed and in the light of the general common knowledge in the field at the date of priority of the present application..

INDUSTRIAL APPLICABILITY - Art. 33 (1) and (4) PCT

9- Claims 1-16, 18-21 and 23-53 appear to be industrially applicable.

Re Item VI
Certain documents cited

10- Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 99 37325	29.07.1999	27.01.1999	27.01.1998 30.12.1998